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Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with β-cyclodextrins

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Abstract

Inclusion complexes of hydrocortisone and progesterone were formed with β-cyclodextrin or 2-hydroxypropyl-β-cyclodextrin. The formation of the complexes was confirmed by differential scanning calorimetry (DSC). The inclusion complexes were incorporated in two types of solid lipid nanoparticles (SLN). In the presence of the complexes the sizes of SLN remained below 100 nm. DSC analysis showed that hydrocortisone and progesterone are dispersed in SLN in an amorphous state. Using the β-cyclodextrin complexes the incorporation of the more hydrophilic drug, hydrocortisone, was higher than that of progesterone. Release of hydrocortisone and progesterone from SLN was lower when they were incorporated as inclusion complexes than as free molecules.

Keywords: Solid lipid nanoparticles; Steroid; β-Cyclodextrin complexes; Inclusion complexation; Release studies

1. Introduction

Solid lipid nanoparticles (SLN) are potential colloidal therapeutic systems able to carry lipophilic or hydrophilic drugs or diagnostics. SLN have been obtained by many researchers using different preparation approaches (Schwartz et al., 1992; Westesen et al., 1993; Domb, 1995). We prepare SLN (Cavalli et al., 1997) by dispersing in water warm oil-in-water (o/w) microemulsions, whose internal phase is composed of solid lipophilic substances with low melting points (50–70°C).

The main aim of this study was to investigate the incorporation into SLN of complexes between two model drugs and two β cyclodextrins, β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin.

In water, cyclodextrins are able to form non-covalent inclusion complexes with lipophilic

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molecules. In the pharmaceutical field, cyclodextrins are used as complexing agents to improve the aqueous solubility of non-polar drugs, and consequently their bioavailability, or to modify some physico-chemical characteristics of drugs by means of inclusion into the hydrophobic cavity of the cyclodextrin (Duchêne, 1987). β-Cyclodextrin is used to prepare oral dosage forms, because of its acute nephrotoxicity, when administered parenterally, while the synthetic derivative, 2-hydroxypropyl-β-cyclodextrin, has a higher water solubility than β-cyclodextrin which decreases its renal toxicity allowing its parenteral administration (Irie et al., 1992; Irie and Uekama, 1997).

Two steroid hormones, hydrocortisone and progesterone, were chosen as model drugs. They are both poorly soluble (water solubility of hydrocortisone $= 1.08 \times 10^{-3}$ M and water solubility of progesterone $= 3.79 \times 10^{-5}$ M) so their inclusion complexes with cyclodextrins have been widely studied to increase their water solubility. Phase solubility analysis (Preiss et al., 1994) has been shown that the molar ratio of cyclodextrin complexes with steroids is 1:2 steroid:cyclodextrin.

A secondary aim was to examine how incorporation of the two model drugs into SLN as cyclodextrin complexes varies the kinetics of drug release.

Inclusion complexes of hydrocortisone and progesterone with β-cyclodextrin and the 2-hydroxypropyl-β-cyclodextrin were prepared by the coprecipitation method (Puglisi et al., 1990). The complexes were characterized by differential scanning calorimetry (DSC) and the drug content determined by chromatographic analysis (HPLC).

To incorporate the drug-cyclodextrin complexes, two types of SLN, A and M, were prepared from two o/w microemulsions using biocompatible and biodegradable components. The two formulations differed only in the lipid matrix used. For comparison purposes, SLN A and M were also prepared, adding hydrocortisone and progesterone, respectively, as free molecules in the warm o/w microemulsions.

DSC analysis was used to investigate the crystalline structure of the SLN and of the two drugs, both incorporated as complexes with the two β-cyclodextrins and as free molecules.

The diffusion of hydrocortisone and progesterone from the different formulations through a hydrophilic membrane was then evaluated.

2. Materials and methods

2.1. Materials

Stearic acid, progesterone, hydrocortisone and butanol were from Fluka (Buchs, Switzerland); Epikuron 200 (soya phosphatidylcholine 95%) was a kind gift from Lucas Mayer (Hamburg, Germany); taurocholate sodium salt was a kind gift from PCA (Basaluzzo, Italy); β-cyclodextrin (βCD) and 2-hydroxypropyl-β-cyclodextrin (2HP-βCD) were from Roquette Italia (Cassano Spinola, Italy); Imwitor 900 (glycerylmonostearate) was a kind gift from Hüls (Witten, Germany). The other chemicals used were of analytical reagent grade.

2.2. Quantitative determination of hydrocortisone and progesterone

The quantitative determination of hydrocortisone and progesterone was performed by reverse-phase high performance liquid chromatography (Loftsson et al., 1994) using a Binary LC 250 pump (Perkin Elmer). Separations were on a 5-μm Ultrasphere ODS column (250×4.6 mm, Beckman). In the case of hydrocortisone analysis, the mobile phase was acetonitrile/tetrahydrofuran/water at a ratio 30:1:69 v/v/v; the flow rate was fixed at 1.2 ml/min and the detector UV (LC 95 UV/Visible detector, Perkin Elmer) at $\lambda = 254$ nm.

In the case of progesterone analysis, the mobile phase was acetonitrile/ethanol/water at a ratio 60:1:39 v/v/v; the flow rate was fixed at 1.5 ml/min and the detector UV (LC-95 UV/Visible detector, Perkin Elmer) at $\lambda = 235$ nm.

2.3. Preparation of the complexes of hydrocortisone and progesterone with β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin

The inclusion complexes of hydrocortisone and progesterone with β-CD and 2HP-βCD were prepared by the coprecipitation method (Puglisi et al., 1990) considering the molar ratio 1:2 drug:β-CD. To obtain the complexes, an excess of hydrocortisone or progesterone was added to β-CD or 2HP-βCD ethanol:water solution (30:70 v/v) and magnetically stirred for 72 h. The residue was filtered, washed and dried in vacuo.

The complexes of hydrocortisone and progesterone with 2-hydroxypropyl-β-cyclodextrin were also prepared by freeze-drying the solutions after the filtration to confirm the complex formation with the coprecipitation method.

The four β-CD complexes were analyzed by differential scanning calorimetry (DSC) to verify complex formation; the concentration of steroids, both in the complexes and in the residual filtrate, was determined by HPLC.

2.4. Determination of the apparent partition coefficient

The apparent partition coefficient of the two drugs alone, or as complexes with the two β-CDs, were determined using stearic acid as lipophilic phase and water as hydrophilic phase to mimic the microemulsion system A.

A known volume of water (pH 5.0) was added to a known volume of stearic acid and the system was stirred with a magnetic bar at 70°C for 30 min. Stearic acid and water were used in the same molar ratio as in the warm microemulsions.

After the separation of the two phases the drug concentration was determined in the aqueous phase by HPLC. The stearic acid/water apparent partition coefficient was then calculated.

2.5. Preparation of solid lipid nanoparticles (SLN)

Two warm oil-in-water (o/w) microemulsion, A and M, were prepared to obtain the SLN.

Microemulsion A contained stearic acid as internal phase (0.70 mmol), while microemulsion M contained a mixture of Imwitor 900: stearic acid at the ratio 20:80 w/w as internal phase (0.70 mmol). Both microemulsions contained Epikuron 200 as surfactant (0.17 mmol), taurocholate sodium salt and butanol as cosurfactants (0.69 mmol and 0.76 mmol, respectively) and distilled water as continuous phase (111.10 mmol). An amount of drug corresponding to 1% w/w calculated on whole microemulsion was added to each formulation. The amount of drug, as free molecules or as complex, was added to melted stearic acid at about 70°C; Epikuron 200, warm water and the cosurfactant were then added to the melted mixture. A clear system was easily obtained under stirring at about 70° C.

From each formulation, A or M, the following microemulsions were prepared:

1. microemulsion without adding any molecules, as a reference;
2. microemulsions with the two β-CDs alone, to verify the stability of the microemulsion system in the presence of cyclodextrins;
3. microemulsions with the two hydrocortisone complexes;
4. microemulsions with the two progesterone complexes;
5. microemulsions with hydrocortisone and progesterone added as free molecules.

Therefore, eighteen different types of SLN were prepared from the above mentioned microemulsions.

SLN were obtained by dispersing the warm microemulsions (about 70°C) in distilled cold water (2–3°C) at a ratio of 1:10 (microemulsion:water, v/v) under mechanical stirring; the dispersions were washed twice with distilled water by diultrafiltration with a TCF2 system (Amicon, Danvers, USA) using a Diaflo YM100 membrane (cut off 100 000 Da).

2.6. Freeze-drying of SLN dispersions

SLN water dispersions were freeze-dried to obtain dry product used for the analytical determination of the drugs and the thermal analysis.

The SLN dispersions were freeze-dried without the addition of a cryoprotectors using a Modulyo freeze-dryer (Edwards, Crawley, UK) and continuing the process for 36 h.

2.7. Preparation of mixtures of SLN components for thermal analysis

Four mixtures of some components of the SLN, in the same molar ratio as in the microemulsions, were prepared for DSC analysis. The mixtures were:

1. stearic acid and hydrocortisone;
2. stearic acid and progesterone;
3. stearic acid:glycerylmonostearate (80:20 w:w) and hydrocortisone;
4. stearic acid:glycerylmonostearate (80:20 w:w) and progesterone.

These mixtures were subjected to the same thermal cycle as the SLN.

2.8. Differential scanning calorimetry (DSC)

DSC analysis was performed using a differential scanning calorimeter DSC 7 (Perkin Elmer) equipped with an instrument controller Tac 7/DX (Perkin Elmer). The instrument was calibrated with indium for melting point and heat of fusion. A heating rate of 20°C/min was employed in the 25–300°C temperature range; analyses were performed under a nitrogen purge; standard aluminium sample pans (Perkin Elmer) were used, and an empty pan was used as reference.

Triple runs were carried out on each sample (inclusion complexes, component mixtures and freeze-dried SLN) to check reproducibility.

2.9. Characterization of SLN

2.9.1. Photon correlation spectroscopy

The average diameter and polydispersity index of all types of SLN A and M (see Section 2.5) were determined by photon correlation spectroscopy (PCS) using an N4 MD instrument (Coulter) at a fixed angle of 90° and at a temperature of 25°C. The polydispersity index is a measure of the size distribution of the nanoparticle population (Koppel, 1972). Each value is the average of ten measurements.

2.9.2. Determination of drugs in SLN

The amount of hydrocortisone or progesterone incorporated in SLN were determined on the freeze-dried SLN. A weighed amount of freeze-dried SLN A or M was dissolved in methanol and the drug concentration determined by HPLC analysis.

2.9.3. Determination of drugs released from SLN

The 'in vitro' release experiments were performed using a multicompartmental rotating cell system; donor and receptor compartments each had a volume of 1.5 ml. A hydrophilic membrane Servapor dialysis tubing (Serva, G), cut off 12 000 Da, was used. The experiment were performed comparing a drug solution, a complex solution and SLN dispersions, at pH 7.4; an equal volume of phosphate buffer pH 7.4 was placed in the receptor compartment. At fixed times, the receptor solution was pipetted out and the drug concentration determined by HPLC.

3. Results

3.1. Characterizations of drug: β-cyclodextrin complexes

The stoichiometry of the four complexes of steroid hormones with β-cyclodextrins was determined by HPLC and the molar ratio 1:2 steroid:βCD was confirmed.

The formation of the inclusion complexes of hydrocortisone and progesterone was investigated by differential scanning calorimetry (DSC). Fig. 1 reports the DSC thermograms of hydrocortisone, β-CD and the inclusion complex of hydrocortisone with β-CD. The DSC curve of hydrocortisone shows a melting peak at 220°C, corresponding to the melting point of the drug, while no peak is present at this temperature in the hydrocortisone:β-CD complex curve. No hydrocortisone melting peak was visible also in the case of the complex of hydrocortisone with 2HP-β-CD complex, either. The DSC analysis of progesterone, and of inclusion complexes of progesterone with β-CD and 2-HP-β-CD, showed the same thermal behaviour; no peak was detectable in the curves of progesterone:β-CD complexes at the melting point of progesterone (127–130°C).

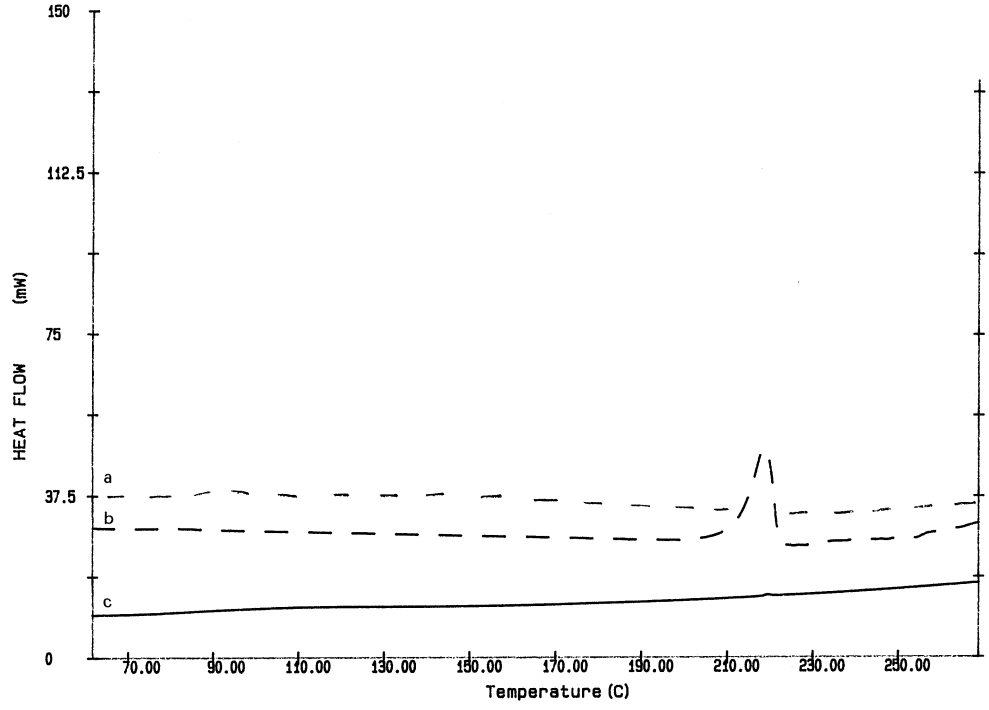

Fig. 1. DSC thermograms of β-CD (a), hydrocortisone (b) and hydrocortisone-β-CD complex (c).

3.2. Apparent partition coefficient of drugs and drug-cyclodextrin complexes in stearic acid/water system

From our experimental data, the apparent partition coefficient of hydrocortisone in the stearic acid/water system was 1.6, and that of progesterone in the stearic acid/water system was 4.5. The apparent partition coefficient of hydrocortisone β-CD complex in the stearic acid/water system was 1.9, while that of progesterone β-CD complex was 6.2; the apparent partition coefficient of hydrocortisone 2HP-β-CD complex in the stearic acid/water system was 2.0, while that of progesterone 2HP-β-CD complex was 6.0.

3.3. Average diameter and polydispersity index of the SLN

The average diameter and the polydispersity index of all types of SLN are reported in Table 1.

The average diameters of SLN A and M with no drug incorporation was 55 and 67 nm, respectively. The addition of the hydrocortisone:β-cyclodextrin complex to the warm microemulsions caused only a slight variation in the diameter of SLN A; a small increase occurred on adding the 2HP-β-CD complex. An increase was, however, detectable for both types of SLN, on adding either complex of progesterone. The SLN increased in size to a greater extent in the presence of the drug as free molecules than as β-CD complex, for both types of SLN.

The polydispersity index values of the SLN dispersions showed the same behaviour of the diameter values (Table 1).

3.4. Percentage of drug incorporated in the different types of SLN

In all warm microemulsions, only 1% w/w of drug was added. This percentage was chosen so as to have a content of β-cyclodextrin not above 20% calculated on the lipid matrix.

Table 1
Average diameter and polydispersity of all types of SLN

SLN	Average diameter (nm)	Polydispersity index
A (blank)	55.0 (±2)	0.23 (±0.02)
M (blank)	67.0 (±3)	0.20 (±0.02)
A βCD	57.0 (±3)	0.23 (±0.02)
M βCD	62.0 (±3)	0.22 (±0.02)
A 2HP-βCD	57.0 (±3)	0.21 (±0.02)
M 2HP-βCD	67.0 (±3)	0.24 (±0.02)
A HC-βCD	60.0 (±3)	0.22 (±0.02)
M HC-βCD	54.0 (±4)	0.21 (±0.03)
A HC-2-HPβCD	90.0 (±4)	0.26 (±0.03)
M HC-2-HCβCD	85.0 (±3)	0.23 (±0.02)
A HC*	80.0 (±5)	0.30 (±0.04)
M HC*	85.0 (±5)	0.26 (±0.03)
A PG-βCD	88.0 (±4)	0.28 (±0.02)
M PG-βCD	78.0 (±4)	0.17 (±0.03)
A PG-2-HPβCD	81.0 (±4)	0.26 (±0.03)
M PG-2-HCβCD	68.0 (±3)	0.23 (±0.03)
A PG*	98.0 (±5)	0.32 (±0.04)
M PG*	85.0 (±6)	0.28 (±0.04)

* Incorporated as free molecules.

Table 2 reports the recovery of hydrocortisone and progesterone incorporated either as complexes or as free molecules in the different types of SLN.

The amount of hydrocortisone incorporated into SLN differed greatly depending on whether drug as free molecule or included in the β-cyclodextrins was used. The same molar amounts of drug, free or as complex, were added to microemulsions A and M. The recovery of hydrocortisone incorporated as complex was larger than that incorporated as free molecules; in the case of the complexes the percentage was higher than 65% for SLN A and about 80% for SLN M, while in the case of free molecules, the percentage of hydrocortisone was 39% for SLN A and 28% for SLN M.

Table 2
Recovery of drugs incorporated into SLN as β-cyclodextrin complexes or free molecule

SLN	Percentages of drug into SLN
A HC-βCD	67.0
M HC-βCD	83.0
A HC-2-HPβCD	67.5
M HC-2-HCβCD	78.0
A HC*	39.0
M HC*	28.0
A PG-βCD	47.5
M PG-βCD	56.0
A PG-2-HPβCD	50.0
M PG-2-HCβCD	55.0
A PG*	54.5
M PG*	53.0

* Incorporated as free molecules.

The percentages of progesterone incorporated as free molecule or as a complex in SLN are also reported in Table 2. The amount of progesterone incorporated as a complexes was not higher than that incorporated as free molecules.

The percentage of drug complex added to the microemulsions can be increased to improve drug incorporation.

3.5. Thermal analysis of freeze-dried SLN

All SLN prepared were analysed by DSC to investigate the crystal habit of the drugs. Hydrocortisone and progesterone as CD complexes did not shown any peak as previously shown (Preiss et al., 1994) and as reported above.

In Fig. 2, the DSC curves of SLN containing hydrocortisone as complexes or as free molecules, are reported.

The thermograms of the freeze-dried SLN containing hydrocortisone or progesterone, either as free molecules or as complexes with the two β-cyclodextrins, did not show the melting peaks for the two drugs at their melting temperatures. This suggest that they are dispersed in the SLN in an amorphous state. To confirm these results DSC analysis of mixtures between stearic acid or stearic acid:glycerylmonostearate (80:20 w:w) and the two drugs were performed. The melting peaks of hydrocortisone and progesterone were present in the thermograms of all the mixtures.

DSC analysis showed that the two drugs are still present in a non crystalline form in the nanoparticles 24 months after SLN preparation.

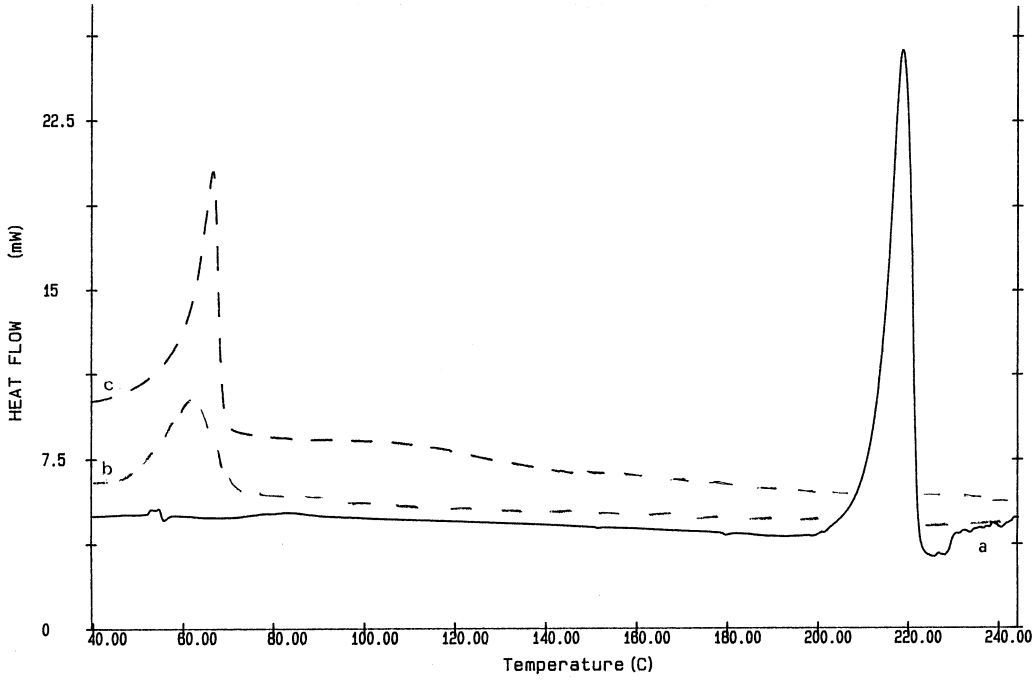

Fig. 2. DSC thermograms of hydrocortisone (a), SLN A containing hydrocortisone as free molecule (b) and SLN A containing hydrocortisone as β-CD complex (c).

3.6. In vitro release kinetics from the different types of SLN

Fig. 3 reports the percentages of hydrocortisone released from the different types of SLN; the curves of hydrocortisone solution and hydrocortisone-β-CD complex solutions are also reported.

The percentage of hydrocortisone released after 120 min from SLN A was 23.0% when the drug was incorporated as free molecules, while it was 11.3 and 9.6% when the drug was incorporated as complex with β-CD or 2HP-CD, respectively.

Release from SLN M was 29.0% as free molecule and 12.2% and 10.7%, respectively, for the β-CD complexes.

Fig. 4 reports the percentage of progesterone released from the different types of SLN; the curves of progesterone β-CD complex solutions are also shown. After 120 min the percentage of progesterone released from SLN A was 10.1%, when the drug was incorporated as free molecules, while it was 5.8 and 5.0% when the drug was incorporated as complex with β-CD or 2HP-CD, respectively.

The release from SLN M was 11.5% for progesterone as free molecule and was 4.0 and 3.5% for progesterone as complex with β-CD or 2HP-CD, respectively.

4. Discussion

Drug-cyclodextrin complexes can be used in dosage forms to take advantages in drug delivery (Rajewski and Stella, 1996). In previous researches cyclodextrin-drug complexes were entrapped into liposomes to include insoluble drugs in the aqueous phase of liposomes (McCormack and Gregoriadis, 1994) and to benefit from both the properties of liposome and cyclodextrin for topical application systems (Becirevic-Lancan and Skalko, 1997). Nanospheres containing progesterone were prepared from an amphiphilic cyclodextrin derivative using the

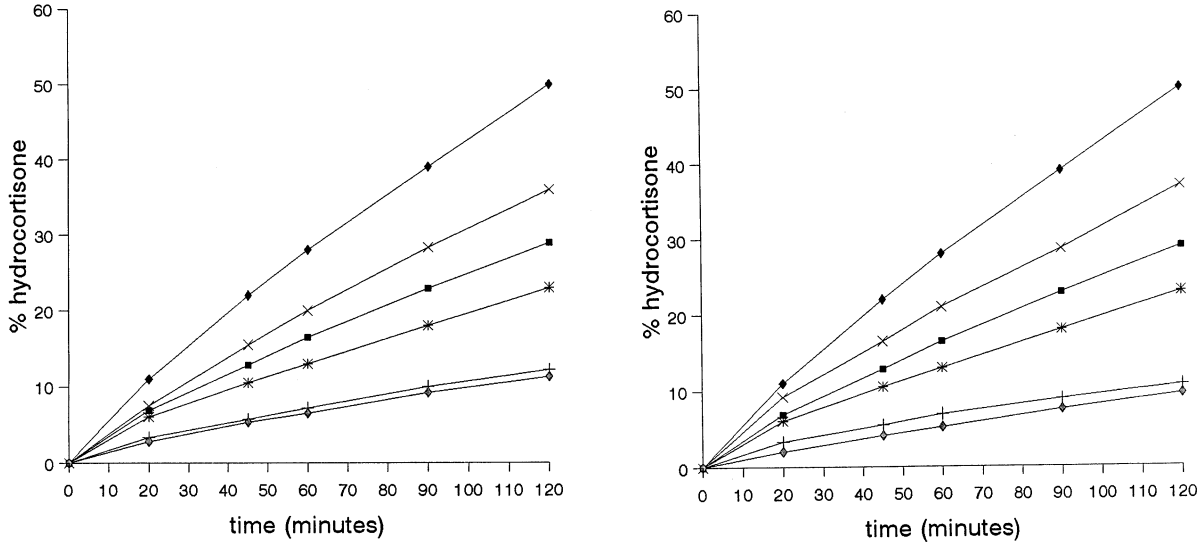

Fig. 3. Percentage of hydrocortisone released vs. time. (left) hydrocortisone-β-cyclodextrin complex, (right) hydrocortisone-hydroxypropyl-β-cyclodextrin complex. ◆, hydrocortisone solution; ×, hydrocortisone-β-CD complex; ■, SLN M containing hydrocortisone as free molecule; *, SLN A containing hydrocortisone as free molecule; +, SLN M containing hydrocortisone as complex; ◇, SLN A containing hydrocortisone as complex.

emulsification evaporation method. (Lemos-Senna et al., 1998).

In this work we studied the incorporation of drug β-CD complexes into SLN and also the different behaviour between two drugs with different lipophilicity.

A preliminary study was performed to verify the stability of microemulsions in the presence of increasing amounts of β-CD or 2-HP-β-CD. The more stable microemulsions and those forming the smallest SLN were chosen for incorporation studies of the drug-β-cyclodextrin complexes.

Two steroid hormones, hydrocortisone and progesterone, were selected as model drugs just because they have similar structures but different lipophilicities as also shown by their partition coefficients in the n-octanol/water system: P_{oct} of hydrocortisone is 35.7, while P_{oct} of progesterone is 7410 (Tomida et al., 1978). The stability constants of the complexes of the two drugs with β-cyclodextrins differ rather considerably: $K_\beta = 1720\ M^{-1}$ for hydrocortisone and $K_\beta = 13\,300\ M^{-1}$ for progesterone (Uekama et al., 1982). The K_β value of progesterone indicates a greater binding of this drug with β-CD, due to the more hydrophobic nature of this molecule, as would be expected from its partition coefficient.

The formation of the inclusion complexes of hydrocortisone and progesterone with β-CD and 2HP-β-CD was confirmed in this study by DSC. The disappearance of the fusion peaks of hydrocortisone and progesterone indicates the presence of an interaction between drugs and the β-CDs, proving the formation of the complexes.

The incorporation of the drug-cyclodextrin complexes determined an appreciable increase of the average diameter values, but the values remained below 100 nm, as shown in Table 1.

The size increase was lower in the case of SLN M, whose lipid matrix was a mixture of glycerylmonostearate:stearic acid (20:80 w/w). The influence of the lipid matrix on the size and physical stability of SLN had been investigated previously, and the choice of the lipid in the microemulsion found to affect SLN diameter (Cavalli et al., 1997). The SLN incorporating hydrocortisone as free molecules had an average diameter above that of SLN containing the complex of hydrocortisone with β-CD; moreover, the polydispersity values of these SLN dispersions also increased, indicating a wider distribution of SLN population.

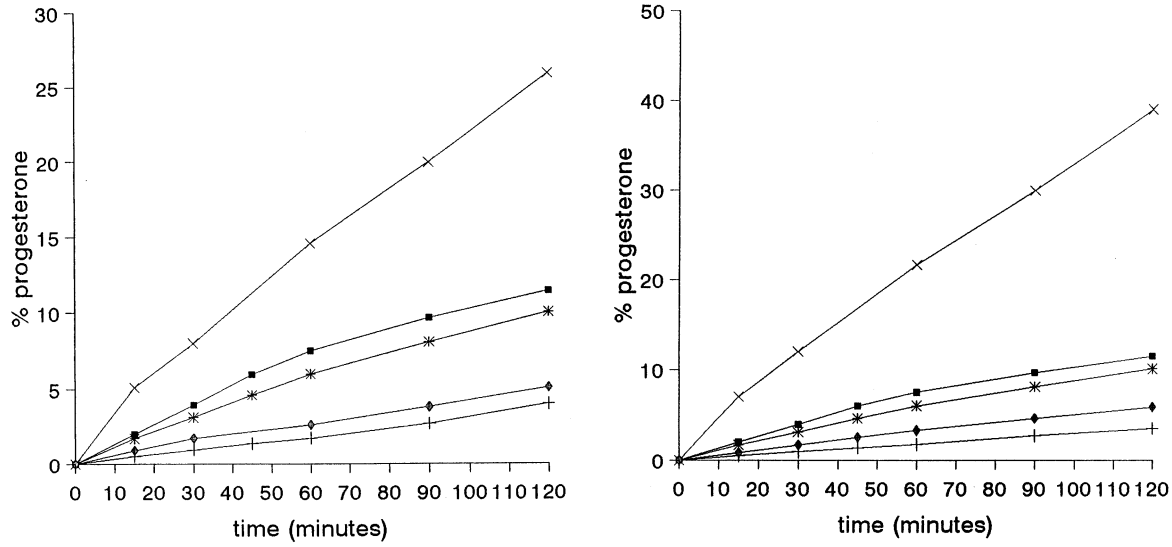

Fig. 4. Percentage of progesterone released vs. time. (left) progesterone β-cyclodextrin complex, (right) progesterone-hydroxypropyl-β-cyclodextrin complex. ×, progesterone-β-CD complex; ■, SLN M containing progesterone as free molecule; *, SLN A containing progesterone as free molecule; +, SLN M containing progesterone as complex; ◇, SLN A containing progesterone as complex.

The SLN incorporating progesterone as free molecules had an average diameter above that of SLN containing the complex of progesterone with β-CD and with 2 HP-β-CD. As previously shown for a series of lipophilic molecules (Cavalli et al., 1998), the size and the structure of the incorporated molecule is a factor affecting SLN size and tends to increase the average diameter and polydispersity index of SLN.

Hydrocortisone and progesterone, incorporated into SLN, either as single molecules or as complexes with the two β-cyclodextrins, did not present a crystalline structure but were dispersed in the SLN in an amorphous form. With regard to the structure of drug-free molecules, a similar thermal behaviour had already been noted in previous studies with other drugs, such as nifedipine, phenothiazine and diazepam (Cavalli et al., 1995; Cavalli et al., 1997), showing that they are in SLN in the amorphous form. This effect on the crystalline habits of drugs may be related to the preparative method of the SLN. SLN were prepared by dispersing warm o/w microemulsions in cold water. In the microemulsion, drugs are partitioned partly in the internal oil phase and partly at the interphase between internal and continuous phase, depending on their lipophilicity; when SLN are formed by a quick quenching of the microemulsion, the presence of the droplet structure of the microemulsion does not allow the drug molecules to nucleate and form the crystal lattice, and consequently the drug molecules remain dispersed in the lipid matrix of the SLN in an amorphous state.

The inclusion complexes favoured the incorporation of hydrocortisone, molecule less hydrophobic than progesterone into SLN as shown in Table 2.

In the case of progesterone, the amount of drug incorporated into SLN as free molecules was very similar to that incorporated as a cyclodextrin complex. This different behaviour between the two drugs studied may be related to their different lipophilicity and consequently to the different partition in the stearic acid used as oil phase in the microemulsions; it was confirmed by the P values obtained in the stearic acid/water system.

The release kinetics of the two drugs from SLN, either free or as a complex, differed depending on the lipophilicity of the drug and the SLN formula-

tion. The release of hydrocortisone and progesterone incorporated into SLN as complexes with β-CD or 2-HP-βCD was slower than that of hydrocortisone and progesterone incorporated as free molecules (Fig. 3).

The release of hydrocortisone from SLN containing the hydrocortisone:β-CDs complexes was higher than that of progesterone from the corresponding SLN, due to the higher hydrophilicity of hydrocortisone and the lower stability constants of its β-CD-complexes.

The influence of β-CDs on release of hydrocortisone and progesterone from SLN can be connected to the different solubilities of their β-CDs inclusion complexes in the lipid matrix, as shown by the apparent partition coefficient values.

The difference in the release kinetics of drugs, depending on whether the steroids are incorporated as free molecules or as an inclusion complex was to be considered. Indeed, the drug incorporated in the SLN as complexes with β-CDs in the SLN delayed notably the release of the drug from the SLN.

In conclusion, the steroid:β-CD inclusion complexes can be incorporated into SLN without great increase of the SLN size. The SLN loading capacity of the more hydrophilic molecules can be increased. By incorporating drugs that are partly in the free state and partly in the form of complexes, and by modifying the formulation of the SLN, it might be possible to modulate the release kinetics of the drug from SLN.

Work is in progress to study the incorporation of highly hydrophilic drugs into SLN using CD complexes.

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